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A Comprehensive Review of Antibiotics in Clinical Trials for Inflammatory Bowel Disease

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Abstract: Although, positive role of special bacteria in induction of Inflammatory Bowel Disease (IBD) including Ulcerative Colitis (UC) and Crohn's Disease (CD) have been demonstrated in several studies but the consensus on etiology of IBD and beneficial effect of antibiotics has not been reached yet. And, also, no well-designed clinical trials in this regard have been done yet. This review focuses on various clinical trials which have been done in according to beneficial use of antibiotics in UC and CD from 1978 to date. For this purpose, all electronic databases such as PubMed, Scopus, Google Scholar and Cochrane library were searched. The results of clinical trials suggested that metronidazole, ciprofloxacin or the combinations of these antibiotics are effective in CD. However, ciprofloxacin is the first choice, because it has good coverage on gram negative and anaerobic bacterium which plays an important role in CD. However, there is a controversy on the use of antibiotics in UC and the efficacy of them in long-term treatment of UC is still in doubt. Various antibiotics such as anti-tuberculosis, macrolides (clarithromycin), fluoroquinolones, 5-nitroimidazoles, rifaximin, rifamycin derivatives (rifampin), aminoglycosides (tobramycin), rifabutin, clofazimine, tetracyclines (tetracycline and doxycycline) and vancomycin have been under attention of researchers in the recent years. Furthermore, other antibiotics with lower cost and adverse effects, effectiveness and availability are the third generation of cephalosporins and gentamicin and also penicillin or clindamycin that should be evaluated in future studies.

Key words: Inflammatory bowel disease, ulcerative colitis, Crohn's disease, clinical trial, antibiotics

INTRODUCTION

Inflammatory bowel diseases: Inflammatory Bowel Diseases (IBD), including Crohn's Disease (CD) and Ulcerative Colitis (UC) are characterized by gastrointestinal (GI) inflammation and some extra-intestinal indicators such as liver complications, arthritis, skin manifestations and eye problems (Williams *et al*., 2008). Site and nature of the inflammatory changes are the main differences between CD and UC (Table 1), in which CD can attack any portion of the GI tract from mouth to anus (skip lesions) and affect the whole bowel wall but a majority of the cases start in the terminal ileum, while, UC is restricted to the mucosa and epithelial lining of the gut, colon and the rectum (Walsh *et al*., 2011).

IBD considered in the past in the developed countries but their prevalence within developing countries has been increasing in the recent years. Also, if the prevalence of CD and UC is quite similar in developed countries such as North America, South America, Europe, Australia and New Zealand, however, there may be differences in developing countries such as Pakistan and India in which much less extra intestinal disease with both UC and CD has been reported. In Pakistan, few patients have perianal or fistulizing disease, however, the age of presentation of CD in India is a decade later than in the West, colonic involvement is also more common and fistulization appears less common in India (Bernstein *et al*., 2010). The incidence of IBD peaks in two age groups: mainly the third decade, with a smaller peak

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Table 1: Summary of the main differences between ulcerative colitis (UD) and Crohn's disease (CD)

Pathophysiology		Symptoms		Management	
CD	UC	CD	UC	CD	UC
Widely regarded as an autoimmune disease	No consensus of autoimmune disease	Defecation is often porridge-like and sometimes steatorrhea, tenesmus is less common but fever and fistulae are common	Defecation is often mucus-like and with blood, tenesmus is more common and fever and fistulae are seen in severe disease	Mesalazine is less useful	Mesalazine is more useful
Cytokine response is associated with T_h17	Cytokine response is ambiguous associated with T_h2	Weight loss is often	Weight loss is more seldom	Antibiotics are effective in long-term	Antibiotics are generally not useful

in the seventh decade. In adults, the prevalence of CD is higher among women but equal in both genders for UC (Kappelman *et al*., 2007). Furthermore, the incidence of CD varies from 0.7 to 14.6 individuals per 100,000 inhabitants, whereas the prevalence of UC varies from 1.5-24.5 individuals per 100,000 inhabitants. About 1.4 million people in the United States (US) suffer from IBD (Carbonnel *et al*., 2009; Lakatos, 2006). Therefore, different treating guideline should be considered in various around of the world that needs further studies.

IBD can induce significant intestinal signs including diarrhea typically having blood and mucus, abdominal pain, vomiting and weight loss (Bernstein *et al*., 2010). Therefore, IBD patients are usually incapable to do their daily works, common relations and experiences (Al-Qabandi *et al*., 2011). Although, the etiology of IBD still remains unknown but the role of genetic, environment, immune response dysregulation, intestinal microbes and Oxidative Stress (OS) have been already demonstrated (Bernstein *et al*., 2010; Rezaie *et al*., 2007; Salari and Abdollahi, 2009). Some studies suggest that infection is the main etiology but distinctive microbes have not been isolated yet (Krisner, 1988). It has been suggested that CD parallels with Johne's disease in cattle which is due to *Mycobacterium avium* subspecies Paratuberculosis (MAP). However, today this hypothesis is not acceptable because MAP is not the only bacterium that is associated with CD and other bacterial strains including *Yersinia enterocolitica*, *Chlamydia trachomatis*, *Listeria* and cell wall deficient pseudomonas are also important (Dalziel, 1913; Sartor, 2005). These organisms as a cause for IBD are still challenging and the evidences are poor but it is still believed that CD and UC are resulted from an irregular immunological reaction to gut microbiota in susceptible host (Abraham and Cho, 2009). It has been demonstrated that the concentration of intestinal microbes in IBD is higher than normal and increases progressively with the severity of the disease (Rahimi *et al*., 2007a). This is important that bowel inflammation does not occur without change in gut bacterial flora as proved in experimental models of colitis (Sellon *et al*., 1998). In the healthy gut, there is a cooperative connection between the host and the gut bacterial flora in which exposure leads to down-regulation of inflammatory genes and inhibiting the immune response of the gut to other pathogens (Hanauer, 2006). Metronidazole, ciprofloxacin or their combinations are commonly used by most clinicians as first-line treatment in patients with perianal disease, in combination with surgical drainage of abscesses (Baumgart, 2012). Therefore, the beneficial role of antibiotics in IBD has been discussed in this review. For this purpose, databases of PubMed, Google Scholar and Scopus were searched from 1978 to February 2012 for clinical trials conducted on UC and CD patients. The search terms were inflammatory bowel disease, IBD, ulcerative colitis, UC, Crohn's disease, CD, antibiotic, antimicrobial agents, antiparasitic agents, antimycobacterials agents, β-lactams, penicillins, cephalosporins, ketolides, carbapenems, tetracyclines, macrolides, aminoglycosides, nitroimidazoles and fluroquinolones. The search strategy was limited to clinical trials and English language.

Pathophysiology of IBD: The pathology of CD is characterized by an intermittent inflammation and skips lesions of transmural bowel wall that can develop to fibrosis, strictures and fistulas. Though, these lesions can occur in any area of the GI tract, they usually take place within the ileum. UC is restricted to the colon and rectum and it involves inflammation of the bowel wall mucosa and submucosa and the lesions can range as far as the cecum (Walsh *et al*., 2011).

While the etiology of IBD is not well known, however, the role of genetic predisposition, environmental triggers, bacteria, Oxidative Stress (OS) and dysregulation of the immune response cannot be ignored (Rezaie *et al*., 2007; Hanauer, 2006; Danese *et al*., 2004). Studies have determined that genetic background can predispose a subset of IBD patients to the progress of disease (Mathew and Lewis, 2004). Studies on genome have discovered more than 40 susceptibility loci for IBD, some of them are distinct for UC or CD and some of them are linked with both (Hakonarson and Grant, 2009). The IBD1 gene encoding the protein NOD2 (also called CARD15) in CD, OCTN1/2 within the IBD5 locus in CD and UC, ATG16L in CD, IRGM1 in CD and IL23R in CD and UC can be noted (Mayer, 2010). Studies have indicated that

defects in NOD2 or OCTN1/2 affect the ability of the host to restrict and eliminate microbes that gain access to gut tissue (Mathew and Lewis, 2004). Interestingly inflammation and lesions generally occur in intestinal regions with the highest bacterial concentration and the patients with IBD typically have greater numbers of adherent bacteria compared to normal subject (Rahimi *et al*., 2007a; Thompson-Chagoyan *et al*., 2005). Intestinal lamina propria contains intestinal epithelia and inflammatory cells which make available an innate immune protection for the GI tract that equilibrates the requirement for immune tolerance of microbiota with the defense against microbial pathogens. Dysfunction at the epithelial border (for example disturbed mucus layer, imperfect tight junctions) may cause failure of tolerance. This dysfunction can trigger innate immune cells, causing them to secrete several cytokines and chemokines to the host commensal microbiota (Abraham and Cho, 2009; Mayer, 2010). It is thought that other immunological factors downstream antigen recognition including over-activity of effector lymphocytes and pro-inflammatory cytokines, failure of regulatory lymphocytes and anti-inflammatory cytokines to control inflammation and resistance of T-cells to apoptosis (Bamias *et al*., 2005). Several studies have demonstrated that Toll-like Receptors (TLRs) represent key mediators of innate host defense in the intestine, involved in maintaining mucosal as well as commensal homeostasis. Recent studies in various experimental models of colitis have helped to reveal the mechanistic importance of TLR dysfunction in IBD pathogenesis. It has been demonstrated that environment, genetics and host immunity form a multidimensional and highly interactive regulatory triad controls TLR function in the intestinal mucosa. Imbalance between these factors may promote aberrant TLR signaling, significantly contributing to acute and chronic intestinal inflammatory processes in IBD (Cario, 2010).

Drugs used in the treatment of IBD: Medical treatment of IBD is rapidly developing with introduction of new biological agents that are likely to modify future therapeutic approaches (Walsh *et al*., 2011). Main objectives of current drug treatments are to maintain the patient in remission and ameliorate the disease's secondary effects, rather than modifying or reversing the underlying pathogenic mechanism (Pithadia and Jain, 2011).

Many drugs and drug classes are available to manage both UC and CD, including 5-amino salicylate (5-ASA) (Nikfar *et al*., 2009; Rahimi *et al*., 2009a), corticosteroids (Rahimi *et al*., 2007b), immunosuppressive agents and anti tumor necrosis factor (TNF-α) (Rahimi *et al*., 2007c; Nikfar *et al*., 2010a; Amini-Shirazi *et al*., 2009), antioxidants (Ebrahimi *et al*., 2008; Khoshakhlagh *et al*., 2007), probiotics (Rahimi *et al*., 2008a; Elahi *et al*., 2008; Nikfar *et al*., 2010b), antibiotics (Loftus *et al*., 2008; Feagan *et al*., 2007) and some herbal medicines as supplemental therapy (Rahimi *et al*., 2009b; Rahimi *et al*., 2010; Abdolghaffari *et al*., 2010; Hasani-Ranjbar *et al*., 2009).

For management of mild to moderate IBD, salicylates are used although they are not without adverse effects. For management of moderate to severe IBD, glucocorticoides and immunosuppressive drugs are usually used (Rahimi *et al*., 2009b). New biological agents target TNF and adhesion proteins for inflammatory cell translocation. However, anti-TNF therapy may increase the risk of infection (Rutgeerts *et al*., 2009; Lakatos and Miheller, 2010; Nikfar *et al*., 2010b) and thus must be used with many caution and as the last options. Antibiotics are recommended in CD patients with perianal disease and fistulas and also in the treatment of C difficile infection (Prantera and Scribano, 2009). Although, antibiotics are often recommended to induce remission in mild to moderate CD, they are also effective for handling fistulas, bacterial overgrowth, abdominal abscesses and infections around the anus and genital areas (Pithadia and Jain, 2011).

Intestinal microflora can be changed by administering antibiotics and prebiotics that contain three species of *Bifidobacterium*, 4 species of *Lactobacillus* and *Streptococcus salivarius* (Prantera and Scribano, 2009; Travis *et al*., 2006) or probiotics (beneficial bacteria) or the combination of these methods (synbiotics). Studies support the protective role of probiotics and prebiotics in IBD or its complications (Salari *et al*., 2012; Ghasemi-Niri *et al*., 2011; Hedin *et al*., 2010; Nikfar *et al*., 2008; Rahimi *et al*., 2008b; Alivanis *et al*., 2010; Jamalifar *et al*., 2011) and even in irritable bowel syndrome (Hosseini *et al*., 2012) and therefore, they can be more effective in combination to antibiotics.

Generally, we can divide the treatment and management of IBD into five steps:

- Administration of oral aminosalicylate including sulfasalazine, mesalamine, balsalazide and olsalazine
- Antibiotics including ciprofloxacin, metronidazole, antituberculosis therapy, macrolides, fluoroquinolones, 5-nitroimidazoles and rifaximin (alone or in combination) can be used. However, the adverse effects of antibiotics including nausea, anorexia, diarrhea and monilial (candidal) infections, peripheral neuropathy (mostly observed with metronidazole) should be concerned in each individual

- Administration of corticosteroids such as intravenous (i.v.) methylprednisolone oral or rectal budesonide (Alivanis *et al*., 2010; Li *et al*., 2008) can be considered
- Administration of immune modifiers including 6-mercaptopurine or azathioprine (1-2 mg kg^{-1} day^{-1}), infliximab (5 mg kg^{-1} at 0, 2 and 6 weeks, followed by 5 mg kg^{-1} every 8 weeks thereafter), adalimumab and natalizumab should be considered (Ford *et al*., 2011; Lichtenstein *et al*., 2006) with adequate care
- Administration of methotrexate (12.5-25 mg $week^{-1}$, p.o. or IM), thalidomide (50-300 mg day^{-1}, p.o.) and IL-11 (1 mg $week^{-1}$, SC) in CD and cyclosporine A (i.v., 2-4 mg kg^{-1} day^{-1}) butyrate enema (rectal, 200 mL day^{-1}) and heparin (SC, 20,000 U day^{-1}) in UC (Lichtenstein *et al*., 2006) should be considered

The common bacteria in IBD: Several studies have shown differences in bacterial diversity between healthy individuals and IBD patients. Overall the result of these studies have shown evidence for a decline in bacterial diversity, an increase in fungal and a decrease in methanogen diversity in GI tract of IBD patients but they could not identify specific bacterial or fungal communities for this disease yet (Scanlan and Marchesi, 2008; Franke *et al*., 2008; Frank *et al*., 2007; Kuehbacher *et al*., 2006; Ott *et al*., 2008; Scanlan *et al*., 2008). Increase of Enterobacteria in patient with IBD has been previously shown (Kotlowski *et al*., 2007). *Mycobacterium avium* subsp. *paratuberculosis*, *Chlamydia pneumoniae*, *Saccharomyces cerevisiae*, *Clostridium difficile*, *Campylobacter jejuni* and adherent invasive *Escherichia coli* (*E. coli*) have all been shown to be potentially infectious organisms in the development of IBD (Reiff and Kelly, 2010; Berg *et al*., 2012; O'Hara *et al*., 2012). Other bacteria which have a positive role in induction of IBD in patients are indicated in Table 2. Some studies have shown that an increase in mucosal populations of adherent invasive *E. coli* which were found prevalent in CD is the strongest evidence of a specific pathogen in human IBD (Sasaki *et al*., 2007; Rhodes, 2007; Darfeuille-Michaud *et al*., 2004).

Commensal microorganisms live with their hosts and are essential for development of a healthy gut. The role of commensal bacteria is to facilitate digestion, absorption and storage of nutrients as well as protection against pathogen colonization through competition for nutrients, secretion antimicrobial substances and micro-niche exclusion. In addition, commensal bacteria promote angiogenesis and development of the intestinal epithelium and have been shown necessary for normal development and function of the immune system (Artis, 2008). Overactive immune response towards commensal bacteria causes initiation and development of IBD. In fact, microbial balance is crucial to protect against bad gram negative pathogens, such as *E. coli* and Pseudomonas (Reiff and Kelly, 2010). Consequently, strong evidence from animal models recommends that the development of IBD is impossible in the presence of normal enteric flora (Triantafillidis *et al*., 2011).

Application of antibiotics in IBD: Most of studies that have indicated the role of special bacteria in induction of IBD, are not well designed. Most of existing clinical trials had small sample size (16 to 213 subjects), short duration (2 to 24 weeks) and methodological bias. In patients with IBD, the rate of Bacteroides, *Escherichia coli* and Enterococci increase in the bowel while Lactobacilli and Bifidobacteria decrease that necessitate use of antibiotics (Triantafillidis *et al*., 2011; Pithadia and Jain, 2011).

Some studies demonstrated that a decrease in mucosal peptide antibiotics (defensins) could be involved in the pathogenesis of IBD. Defensins are antimicrobial peptides made at a range of epithelial exteriors that their highest function is to retain equilibrium between protection from pathogens and tolerance to normal flora. It has been advised that diminished expression of defensins compromises host immunity resulting in inflammation. This deficiency may be due to change in the intracellular transcription of NF-κB and the intracellular peptidoglycan receptor NOD2. The beneficial effect of antibiotics in CD patients exhibits the theory of the presence of weakened mucosal antibacterial motion. Although recent studies suggest that defensin deficiency might be a result of mucosal surface damage in inflammatory course, it still needs to be clarified by further studies (Triantafillidis *et al*., 2011; Wehkamp *et al*., 2005; Ramasundara *et al*., 2009; Fellerman *et al*., 2003).

Generally, antibiotic can be used in IBD for numerous aims including as an assistant in the company of other medicines for handling of active IBD, as a management for a definite impediment of CD and as prophylaxis for disease relapse in postoperative CD (Triantafillidis *et al*., 2011). The conditions that use of antibiotics cannot be declined include (*C. difficile* and so forth) (Sartor, 2004):

- Phlegmon of intra-abdominal, hepatic or perianal abscesses and inflammation
- Fistulae (perianal, enteroenteric, enterocolonic, enterocutaneous and enterovesical)
- Anal fissures
- Small intestinal bacterial overgrowth secondary to strictures, loss of ileocecal valve, enteroenteric and enterocolonic fistulae

Table 2: Possible bacterium which has a positive role in IBD

Bacterium	Antibiotic of choice	Alternative	Comments	References
Escherichia coli	Third generation of cephalosporin	First to second generation of cephalosporin, GM	Allergic reaction including anaphylaxis, urticaria, serum sickness, rash, diarrhea and fever may be induced with cephalosporins. Gram-negative organisms including *E. coli* have reported high susceptibility to AM and third-generation cephalosporin's and low susceptibility to AMP, GM and CTX. Therefore, the use of CTX or AMP as the first choice in prophylactic and empirical treatment should be reconsidered	Yoon *et al.* (2011) and Koda-Kimble *et al.* (2009)
Clostridium difficile	MTZ	VCM, RFX, FDX	MTZ and VCM are equally effective for the treatment of mild CDAD but VCM is superior for treating patients with severe CDAD. FDX is better or have equal effect as VCM. Ototoxicity, nephrotoxicity and hypotension, flushing adverse effect induced with VCM should be concerned	Teasley *et al.* (1983), Zar *et al.* (2007) Epstein and Golan (2012) and Koda-Kimble*et al.* (2009)
Mycobacterium avium subspecies paratuberculosis	RFB+Macrolide (CLR or AZ)	ND	MAP is not susceptible to antituberculosis drugs in which can generally kill *M. tuberculosis*	Gui *et al.* (1997)
Chlamydia pneumoniae	DOX	ERM, TE	Rash, fever, anaphylaxis, urticaria, nausea, photosensitivity, hepatitis and diarrhea may be induced with TE administration. TE should be avoided in pediatrics, pregnancy, breast feeding and in patients who have lower renal function, however, less adverse effect induced with DOX	Burillo and Bouza (2010), and Koda-Kimble*et al.* (2009)
Chlamydia Trachomatis	DOX	ERM, AZ	AZ has less nausea problem than ERM	Koda-Kimble *et al.* (2009)
Yersinia enterocolitica	DOX+AMG	CTX, FQ, CTX and CL.	*Y. enterocolitica* is usually resistant to PEN-G, AMP and CET due to beta-lactamase production	Bottone (1997)
Listeria monocytogenes	AMP+GM, AMC and CL	CTX, AZ, VCM, ERM, TE	CTX has been shown good respond in PEN allergic patients	Ruiz-Bolivar *et al.* (2011)
Campylobacter jejuni	FQ, ERM	TE, CIP, ERM, AZ or NRF 2011	Nearly 90% of *C. jejuni* infection is responded to CIP treatment. Replacement of electrolyte and fluid may be required for serious infection	Maragkoudakis *et al.* (2011)
Fusobacterium varium	PEN and AMX	MTZ, TE and CL	No serious drug-related toxicity was observed during the 2-week antibiotic (AMX, MTZ and TE) combination therapy against *F. varium* in patients with chronic or active UC However, the risk of nausea, vomiting, burning stomach, cholestatic jaundice and ototoxicity should be evaluated in administration of CL	Ohkusa *et al.* (2005) and Koda-Kimble *et al.* (2009)

AM: Amikacin, GM: Gentamicin, CTX: Cotrimoxazol, AMP: Ampicillin, MTZ: Metronidazole, VCM: Vancomycin, RFX: Rifaximin, FDX: Fidaxomicin, CDAD: Clostridium difficile associated diarrhea, ND: Not determined, ERM: Erythromycin, RFB: Rifabutin, MAP: *Mycobacterium avium subspecies paratuberculosis*, DOX: Doxycycline, CLR: Clarithromycin, TE: Tetracycline, AZ: Azathioprine, AMG: Aminoglycoside, AMC: Amoxicillin-clavulanic acid, FQ: Fluoroquinolones, CTX: Ceftriaxone, CAM: Chloramphenicol, CIP: Ciprofloxacin, CL: Clindamycin, PEN: Penicillin, NRF: Norfloxacin, CET: Cephalotin, AMX: Amoxicillin

- Postoperative infections
- Toxic megacolon
- Secondary infections

Mechanisms of action of antibiotics in IBD include (Sartor, 2004):

- Reduction of luminal and adherent mucosal bacterial foci
- Selective elimination of pathogenic luminal bacteria
- Reduction of tissue invasion, microabscesses and secondary bacterial proliferation adjacent to mucosal ulcers and fistulae
- Reduction of bacterial translocation and systemic dissemination of possible bacteria

The use of antibiotics as principal or adjuvant treatment of UC and CD is still debated. Even though the systemic use of antibiotics against IBD can act against enteric commensal bacteria but controlled clinical trials support use of these agents (Sartor, 2004).

Diverse factors may be measured in IBD clinical trials include CD activity index (CDAI) and Serum Orosomucoid (SO) which can be measured to estimate the improvement of disease activity (mean CDAI; 217; range, 160-305) (Colombel *et al*., 1999). Other factors include median pre-treatment Harvey Bradshaw index (HBI) (9; range 5-16) and median serum C-reactive protein (CRP) (21.5 mg L^{-1}; range <5-117) and production of provocative cytokines (Leiper *et al*., 2000).

Antibiotics in CD; current clinical trials: In recent times, several clinical trials have been published on the use of broad-spectrum antibiotics in CD patients. The antibiotic used so far in patients with CD include metronidazole, rifaximin, clarithromycin, ciprofloxacin, clofazimine and anti-tuberculosis drugs. Ciprofloxacin and metronidazole or their combination are considered as standard for prompting remission in CD while ciprofloxacin is the first choice because it has good coverage on gram negative and anaerobic bacteria such as *E. coli* (Sreedhar *et al*., 2008). A systematic review and meta-analysis of Randomized Controlled Trials (RCTs) by Khan *et al*. (2011) showed the benefit of antibiotics in treatment of IBD. They were effective in both remission of active CD (Relative Risk (RR) of active disease not in remission was 0.85) and conservation of CD (RR of relapse was 0.62) (Khan *et al*., 2011). Anti-tuberculosis, macrolides, fluroquinolones, 5-nitroimidazoles, rifaximin and rifamycin derivatives were tested in this study (Khan *et al*., 2011). Cotrimoxazole and tetracycline are other antibiotics were also used for CD (Triantafillidis *et al*., 2011).

As we mentioned in Table 3, rifaximin as a rifamycin analog with a broad spectrum of activity in form of rifaximin-extended intestinal release has been used in CD and the results showed improvement in remission as CDAI reduced. Also metronidazole was used in CD as monotherapy or in combination with ciprofloxacin and cotrimoxazole in several clinical trials successfully and led to remission and decrease of CDAI. Results of the clinical trials demonstrated that ciprofloxacin is an effective drug in a proportion of patients with active CD mainly located in the colon. Clarithromycin as a broad-spectrum antibiotic has been used in CD but it was found ineffective in active CD. It is notable that use of clarithromycin in combination with rifabutin has been good in decreasing CDAI. Although, it has been shown that antituberculosis compounds are ineffective in CD but rifabutin in combination with clofazimine and clarithromycin reduced inflammation in CD.

Further clinical trial studies about antibiotic therapy in CD are summarized in Table 3.

Antibiotics in UC; current clinical trials: In comparison to CD, there are a few studies about the advantageous of antibiotics in UC where they seem ineffective for long-term treatment (Table 1) in spite of implicating of bacteria such as Enterococci, Peptostreptococci and Enterobacteria which live on the lining of the bowel being involved in UC. The failure of antibiotics may possibly return to poor identification of involved bacteria in UC and unsuitable pick of antibiotics. Nevertheless, most of studies have reported the benefit of ciprofloxacin, metronidazole and tobramycin in UC (Mantzaris *et al*., 1994, 2004; Madden *et al*., 1994; Chiba *et al*., 2011).

As we mentioned in Table 4, use of amoxicillin in combination with tetracycline and metronidazole in UC improved clinical symptoms, reduced Clinical Activity Index (CAI) and retained disease in remission. Furthermore, use of amoxicillin with clavulanic reduced production of inflammatory cytokines. Ciprofloxacin has been investigated in patients with UC with diverse results and needs further studies but in overall it seems effective. Rifaximin was also studied in patients with UC and showed no significant differences in clinical efficacy however it improved stool frequency, rectal bleeding and sigmoidoscopic score. Investigations demonstrated that use of metronidazole in UC in conjunction with

Table 3: Summary of clinical trials of antibiotic therapy in CD

Study design	Interventions	Duration	Adjunctive therapy	N	Outcome	References
Double blind randomized controlled trial	RFX-EIR (800, 1600 and 2200 mg day^{-1}, p.o.)	12 weeks	Stable dose of Mesalamine, Thiopurines, MTX (12.5-25 mg $week^{-1}$, p.o. or IM), Probiotics and Anti-diarrheas	402	Improvement in remission rate of 62, 54 and 47% with different antibiotic doses of 400, 800 and 1200 mg, respectively, has been achieved. Dose 800 mg also induced remission with few adverse events	Prantera *et al.* (2012)
Randomized controlled trial	MTZ (10% ointment, 2.1 g day^{-1}, Perianal) vs. placebo	4 weeks	Stable dose of 5-ASA, corticosteroids, MTX,antibiotics, CS (2-4 mg kg^{-1} day^{-1}, i.v.) and IFX	74	A reduction in perianal CDAI score of at least 5 points in antibiotic group was recorded	Maeda *et al.* (2010)
Randomized controlled trial	MTZ (1000 mg day^{-1}, p.o.), CIP (1000 mg day^{-1}, p.o.) vs. placebo	10 weeks	AZ and 6-MP, MTX, MMF, Steroids (Conventional Corticosteroids or BUD)	10 (CIP) and 7 (MTZ)	Improvement in remission rate occurred in 3 patients (30%) with CIP but no patients (0%) with MTZ	Thia *et al.* (2009)
Randomized controlled trial	CLR (1 g day^{-1}, p.o.) vs. placebo	3 months	PDN (>10 mg) or >BUD (3 mg for more than a month), AZ or 6-MP at least 3 months, 5-ASA for at least 1 month (at stable dose)	41	No significant difference in improvement of remission (26%) and response (27%) rates or CDAI ((35 (80) for CLR and -2 (114) for placebo) were recorded at 3 months of antibiotic therapy	Leiper *et al.* (2008)
Non randomized open label study	RFB (300 mg day^{-1}, p.o.), CLR (500 mg day^{-1}, p.o.) and CLO (100 mg day^{-1}, p.o.)	6 months	ND	20	Clinicca remission, clinical improvement and endoscopic improvement were evaluated; however, no outcome was reported. It remains at phase 4 of clinical trial	Koch (2007)
Randomized controlled trial	RFB (600 mg day^{-1}, p.o.), CFZ (100 mg day^{-1}, p.o.) and CLR (1 g day^{-1}, p.o.)	6 months	Mesalazine, PDN, AZ, BS, OLZ, Zinc, Iron tablets, MTX and NAG	52	Reduction in inflammation (38.5%) and scarring healing (56.4%) occurred in CD patients to 9 years	Borody *et al.* (2007)
Randomized controlled trial	CLR (750 mg day^{-1}, p.o.), RFB (450 mg day^{-1}, p.o.), CFZ (50 mg day^{-1}, p.o.) vs. placebo	16 weeks	PDN (40 mg day^{-1}), AZ/6-MP, 5-ASA	213	Improvement in remission rate (66%) by using this combination therapy for up to 2 years	Selby *et al.* (2007)
Open label randomized controlled trial	CLR (400 mg day^{-1}, p.o.)	4-24 weeks	AZ	14	Clinical improvement in 57.1 and 42.9% of patient occurred within 4 and 12 weeks, respectively. Furthermore, remission remained after 24 weeks	Inoue *et al.* (2007)
Randomized controlled trial	RFX (800-1600 mg day^{-1}, p.o.) vs. placebo	12 weeks	Immunosuppressors and 5-ASA derivatives	83	Improvement in remission and response rates were achieved vs. placebo	Prantera *et al.* (2006)
Randomized controlled trial	CIP (1000 mg day^{-1}, p.o.)	12 weeks	IFX (5 mg kg^{-1} at weeks 6, 8 and 12, i.v.)	13	In the CIP group, 10 different genera of MOs were identified,while 13 genera could be identified in the placebo group, therefore, antibioti treatment should be directed toward these MOs	West *et al.* (2005)
Open label study	RFX (600 mg day^{-1}, p.o.)	16 weeks	Corticosteroids, 6-MP or AZ	29	Reduction in CDAI score of 43% was achieved at the end of month 4	Shafran and Johnson (2005)

Table 3: Continue

Study design	Interventions	Duration	Adjunctive therapy	N	Outcome	References
Randomized controlled trial	CIP (1000 mg day^{-1}, p.o.) vs. placebo	12 weeks	IFX 5-mg kg^{-1} in week 6, 8 and 12	24	Reduction in number of draining fistulae of 73% occurred in antibiotic group at 18 week. Improvement in the perianal CGAI score was recorded in antibiotic group	West *et al.* (2004)
Randomized controlled trial	CIP (500-1000 mg day^{-1}, p.o.), MTZ (1000-1500 mg day^{-1}, p.o.)	8 weeks	AZ (2–2.5 mg kg^{-1} day^{-1})	52	Complete healing (25%) occurred in antibiotic group and 50% of patients responded to treatment at week 8. Furthermore, reduction in the perianal CDAI was recorded.	Dejaco *et al.* (2003)
Double blind trial	CIP (1000 mg day^{-1}, p.o.), MTZ (1000 mg day^{-1}, p.o.)	8 weeks	BUD (9 mg day^{-1}, p.o.)	134	No effective intervention was recorded when CIP and MTZ was added to budesonide, however, this antibiotic combination improved outcome (53%) when there is involvement of the colon vs. placebo (25%)	Steinhart *et al.* (2002)
Randomized controlled trial	CIP (1000 mg day^{-1}, p.o.) vs. placebo	6 months	6-MP or AZ	47	Reduction in CDAI scores occurred in antibiotic group (112) vs. placebo (205)	Arnold *et al.* (2002)
Randomized controlled trial	CLR (500 mg day^{-1}, p.o.), RFB (300 mg day^{-1}, p.o.)	4-17 months	Probiotic	36	Reduction in CDAI by 58.3% occurred in CD patients and they had no need to other medications	Shafran *et al.* (2002)
Randomized controlled trial	CLR (1000 mg day^{-1}, p.o.), ETB (15 mg day^{-1}, p.o.)	3 months	ND	31	No difference was seen between the treatment or placebo groups in the mean HBI	Goodgame *et al.* (2001)
Uncontrolled open label study	CLR (500 mg day^{-1}, p.o.)	4-12 weeks	PDN (10 mg day^{-1}, p.o.), 5-ASA, AZ	25	Reduction in HBI (5 (range 0-18)) and CRP (17 mg L^{-1} (range<5-157)) By 4 weeks antibiotic therapy. However, the median HBI was 5(range 0-18) an median CRP was 14.5 mg L^{-1} (range<5-157) by 12 weeks	Leiper *et al.* (2000)
Randomized controlled trial	CIP (1 g day^{-1}, p.o.)	6 weeks	Mesalazine (Pentasa 4 g day^{-1}, p.o.)	40	Improvement in remission was achieved in 10 patients (56%) treated with antibiotic and 12 patients (55%) treated with mesalazine, therefore, CIP 1 g day^{-1} is as effective as mesalazine 4 g day^{-1} in treating mild to moderate flare-up of CD	Colombel *et al.* (1999)
Randomized controlled trial	Antituberculous treatment (Following standard treatment including 5-ASA preparations, Steroids, Immunosuppressants and Antibiotics)	2 years, patient followed for 5 years	Various combinations of 5-ASA preparations, steroids, Immunosuppressan, Antibiotics in routine administration way	130	No beneficial or disadvantage evidence of antituberculous chemotherapy was recorded	Thomas *et al.* (1998)
Uncontrolled study	CIP (1000 mg day^{-1}, p.o.), MTZ (750 mg day^{-1}, p.o.)	10 weeks	PDN (15 mg day^{-1}, P.o.), 5-ASA	72	Improvement in clinical remission (68%) and clinical response (76%) occurred	Greenbloom *et al.* (1998)
Clinical practice, few controlled trials	CIP (1000 mg day^{-1}, p.o.), MTZ (1000 mg day^{-1}, p.o.)	12 weeks	MP (0.7-l mg kg^{-1} day^{-1})	41	Improvement in clinical remission of 45.5% in antibiotic group and 63% with steroid group was obtained. Reduction in CDAI (<or = 150) occurred	Prantera *et al.* (1996)

Table 3: Continue

Study design	Interventions	Duration	Adjunctive therapy	N	Outcome	References
Randomized controlled trial	RFP (450 mg day^{-1} for patients weighing less than 50 kg and 600 mg for those 50 kg or more), INH (300 mg day^{-1}, p.o.), ETB (15 mg day^{-1}, p.o.) vs. placebo	12 months	PDN	130	No differences in body weight, CDAI, albumin blood values, hemoglobin, white cell count and platelets were recorded between groups	Swift *et al.* (1994)
Randomized controlled trial	RFP (600 mg day^{-1}, p.o.), ETB(15 mg day^{-1}, p.o.), DDS (100 mg day^{-1}, p.o. for 6 days per week), CFZ (100 mg/2day, p.o.) vs. placebo	2 months	PDN (0.7-1 mg kg^{-1} day^{-1})	40	No endoscopic or radiologic healing occurred. Furthermore, improvement in clinical symptoms and maintenance of remission were achieved in CD patients	Prantera *et al.* (1994)
Randomized controlled trial	FA (1500 mg day^{-1}, p.o.)	8 weeks	PDN, SSZ or Mesalazine	8	Improvement of 63% (5 patients) occurred during FA treatment, 3 at two weeks and 2 after four weeks	Langholz *et al.* (1992)
Double blind cross over trial	MTZ (20 mg kg^{-1} day^{-1} or 10 mg kg^{-1} day^{-1}, p.o.) vs. placebo	16 weeks	ND	105	Reduction in CDAI.	Sutherland *et al.* (1991)
Randomized controlled trial	CFZ (100 mg day^{-1}, p.o.) vs. placebo	8 months	PDN (40 mg day^{-1})	49	Improvement in remission rate (32.65%) and reduction of CDAI was recorded	Afdhal *et al.* (1991)
Randomized controlled trial	VN, (1800-2400 mL day^{-1}, p.o.), FM (2000 mg day^{-1}, p.o.), COL (6 mega U/d, p.o.) and NYS (4 mega U/d, p.o.)	10 days	PDN (0.5 mg kg^{-1} day^{-1}, p.o.)	37	Improvement of 43.24% was achieved In antibiotic plus elemental diet group(16 patients) and also reduction in CDAI, ESR and fecal granulocyte excretion were recorded	Saverymuttu *et al.* (1985)
Prospective randomized trial	MTZ (800 mg day^{-1}, p.o.)+CTX (1920 mg day^{-1}, p.o.) vs. placebo	1 month	ND	72	No significant effect on fecal flora or hematologic parameters including hemoglobin, albumin, CRP was recorded; therefore, antibiotics have little therapeutic potential for relapse of intestinal CD	Ambrose *et al.* (1985)
Randomized controlled trial	ETB (15 mg day^{-1}, p.o.)+RFP (10 mg day^{-1}, p.o.) vs. placebo	2 years	PDN (Mean dose 8.2 mg, range 2.5-30 mg day^{-1}). SSZ (1.5-4 g day^{-1})	27	No significant difference was recorded.	Shaffer *et al.* (1984)
Double blind cross over trial	MTZ (800 mg day^{-1}, p.o.)	4 months	SSZ	78	Reduction in CDAI and orosomucoid plasma level was recorded; Data show slightly more effectiveness of antibiotic therapy than SSZ	Ursing *et al.* (1982)
Double blind cross over trial	MTZ (1000 mg day^{-1}, p.o.)	2 months	ND	22	No significant effect was recorded on the overall clinical condition in patients; however, reduction in hemoglobin rose and ESR occurred during antibiotic treatment.	Blichfeldt *et al.* (1978)

RFX-EIR: Rifaximin-extended intestinal release, PO: Per oral, IV: Intravenous, N: Number of patients, AMX: Amoxicillin, TE: Tetracycline, MTZ: Metronidazole, CIP: Ciprofloxacin, MTX: Methotrexate, 5-ASA: Aminosalicylates, CS: Cyclosporin, IFX: Infliximab, AZ: Azathioprine, 6-MP: 6-mercaptopurine, ND: Not determined, MMF: Mycophenolate mofetil, PDN: Prednisolone, BUD: Budesonide, RFX: Rifaximin, CLR: Clarithromycin, OLZ: Olsalazine, NAG: *N*-acetyl glucosamine, BS: Bismuth subcitrate, RFB: Rifabutin, CFZ: Clofazimine, MP: Methylprednisolone, MO: microorganism, ETB: Ethambutol, HBI: Harvey Bradshaw index, CDAI: Crohn's disease activity index, RFP: Rifampicin, CLO: Clofazimine, INH: Isoniazid, DDS: Dapsone, FA: Fusidic acid (an antibiotic with T-cell specific immunosuppressive effects similar to those of cylosporin): VN: Vivonex, FM: Framycetin, COL: Colistin, NYS: Nystatin, SSZ: Sulfasalazine, CTX: Cotrimoxazol

Table 4: Summary of clinical trials of antibiotic therapy in UC

Study design	Interventions	Duration	Adjunctive therapy	N	Outcome	References
Randomized controlled trial	AMX (1500 mg day^{-1}, p.o.), TE (1500 mg day^{-1}, p.o.), MTZ (750 mg day^{-1}, p.o.)	2 weeks	Mesalamine (4 g day^{-1}, p.o.)	48	Improvement in clinical symptoms (54.2-75.0%), remission rate (31.3-37.5%), endoscopic (56.3%) and histological evaluation (52.1%) and steroid withdrawal in steroid-dependent UC patients 6 and 12 months after antibiotic treatment	Terao *et al.* (2011)
Randomized controlled trial	AMX (1500 mg day^{-1}, p.o.), TE (1500 mg day^{-1}, P.o.), MTZ (750 mg day^{-1}, p.o.)	2 weeks	PDN (10-30 mg day^{-1} (i.v. or p.o.)	25	CAI and endoscopic score were significantly decreased 3 and 12 months after antibiotic treatment. At 12 months histological scores were also significantly decreased	Uehara *et al.* (2010)
Double blind placebo controlled multicenter trial	AMX (1500 mg day^{-1}, p.o.), TE (1500 mg day^{-1}, p.o.), MTZ (750 mg day^{-1}, p.o.) vs placebo	2 weeks	5-ASA, SSZ, Steroids and Probiotics	105	Improvement in remission rates (19.0%) and endoscopic scores were recorded with antibiotics vs. placebo (15.8%) at 3 month	Ohkusa *et al.* (2010)
Randomized controlled trial	AMX (1500 mg day^{-1}, p.o.), TE (1500 mg day^{-1}, p.o.), MTZ (750 mg day^{-1}, p.o.)	2 weeks	ND	49	Improvement in clinical symptoms and endoscopic scores was recorded 3 months after antibiotic treatment. Reduction in cytokine levels (IL-8), CRP and MIP-1 was also recorded	Sato *et al.*(2009)
Randomized controlled trial	AMX (1500 mg day^{-1}, p.o.), TE (1500 mg day^{-1}, p.o.), MTZ (750 mg day^{-1}, p.o.)	2 weeks	ND	20	Improvement in clinical assessment, colonoscopic and histological scores and reduction in terminal restriction fragment length polymorphism and only *F. varium* was recorded with antibiotic treatment	Nomura *et al.* (2005)
Randomized controlled trial	AMX (1500 mg day^{-1}, p.o.), TE (1500 mg day^{-1}, p.o.), MTZ (750 mg day^{-1}, p.o.)	2 weeks	SSZ (2 g day^{-1}, p.o.), 5-ASA, PDN and/or Probiotics at a stable dose HCT (400 mg day^{-1}, i.v.),	20	Improvement in clinical activity, endoscopic and histological scores and remission rate was recorded with antibiotics vs. the control group	Ohkusa *et al.* (2005)
Randomized controlled trial	CIP (800 mg day^{-1}, i.v.) vs. placebo	10 days	HCT (200 mg day^{-1}, Enema)	55	No significant augmentation was achieved with antibiotic and corticosteroids therapy in acute or severe UC patients	Mantzaris *et al.* (2001)
Randomized controlled trial	RFX (500 mg day^{-1}, p.o.) vs. placebo	10 days	Steroids tapered	28	Reduction in stool frequency, rectal bleeding and sigmoidoscopic scores occurred by antibiotic	Gionchetti *et al.* (1999)
Randomized controlled trial	AMC (1500+ 750 mg day^{-1}, respectively, p.o.) vs. placebo	5 days	MP (40 mg day^{-1}, i.v.)	30	Reduction in HBT excretion and cytokine (IL-8) production or other inflammatory mediators was recorded with antibiotic treatment	Casellas *et al.* (1998)
Randomized controlled trial	CIP (1000-1500 mg day^{-1}, p.o.) vs. placebo	6 months	PDN (0.75 mg kg^{-1} for 4 weeks and was continued at 0.5 mg kg^{-1} during the next 4 weeks, 0.25 mg kg^{-1} up to 12 weeks), Rectal steroids, Mesalamine (1600 mg day^{-1})	83	Improvement in endoscopic and histological findings was recorded by antibiotic at 3 months but not at 6 months (with treatment rate failure of 21%)	Turunen *et al.* (1998)
Randomized controlled trial	CIP (500 mg day^{-1}, p.o.) vs. placebo	14 days	PDN (initial dose 20 or 40 mg for mild and moderately active ulcerative colitis, respectively), BMZ (2 g day^{-1}, Enemas) for 7-9 weeks and OLZ (1 mg day^{-1}, p.o.)	70	Improvement in remission rate (34.2%) was recorded	Mantzaris *et al.* (1997)

Table 4: Continue

Study design	Interventions	Duration	Adjunctive therapy	N	Outcome	References
Randomized controlled trial	MTZ (1500 mg, i.v.), TOB (4 mg kg^{-1}, i.v.)	10 days	HCT (400 mg day^{-1}, i.v.) and HCT (200 mg day^{-1}, Enemas)	39	No significant improvement in remission rate was achieved with antibiotic treatment (24 patients (70.5%)) vs. placebo (26 patients (72%))	Mantzaris *et al.* (1994)
Randomized controlled trial	TOB (360 mg day^{-1}, p.o.) vs. placebo	7 days	PDN (60 mg day^{-1}, p.o.), PDN (30 mg day^{-1}, p.o.), HCT (200 mg day^{-1}, Enema)	81	No significant difference in the relapse rates was achieved in two groups	Lobo *et al.* (1993)
Randomized controlled trial	TOB (360 mg day^{-1}, p.o.) vs. placebo	7 days	SSZ, HCT enemas, PDN (30-60 mg day^{-1}, p.o.) or intravenous equivalent of HCT/d	84	Improvement in symptomatic remission (74%) and histological scores was recorded with antibiotic treatment	Burke *et al.* (1990)
Randomized controlled trial	MTZ (1500 mg day^{-1}, i.v.) vs. placebo,	5 days	MP (64 mg day^{-1}, i.v.), HCT (200 mg day^{-1}, Enema)	39	Improvement in remission rate (74%) with antibiotic treatment was achieved at the end of five days	Chapman *et al.* (1986)
Randomized controlled trial	VCM (2000 mg day^{-1}, i.v.) vs. placebo	7 days	PDN (40 mg day^{-1}, p.o.)	40 (33 UC, 7 CD)	Reduction of operative intervention requirement in UC patients occurred	Dickinson *et al.* (1985)

PO: Per oral, IV: Intravenous, N: Number of patients, SD: Study design, AMX: Amoxicillin, TE: Tetracycline, MTZ: Metronidazole, CAI: Clinical activity index, CIP: Ciprofloxacin, PDN: Prednisolone, HCT: Hydrocortisone, SSZ: Sulfasalazine, RFX: Rifaximin, AMC: Amoxicillin-clavulanic acid, MP: Methylprednisolone, BMZ: betamethasone, OLZ: Olsalazine, TOB: Tobramycin, VCM: Vancomycin, MIP-1: Macrophage inflammatory protein-1, CRP: C-reactive protein, IL: interleukin, HBT: HBT (hydrogen breath test) is a simple and non-invasive test for clinical diagnosis of IBD patients which is performed after a short period of fasting (typically 8–12 hours), EC: enteric-coated

corticosteroids produced no better results when compared with placebo plus corticosteroids in inducing remission. It was reported that use of metronidazole in combination with tobramycin showed no significant improvement in remission rate.

Further clinical trials about antibiotic therapy in UC are summarized in Table 4.

CONCLUSIONS

Taking collectively, undesirable effects of aerobic and anaerobic bacteria in etiology of IBD cannot be neglected (Artis, 2008) and thus it is not surprising to see usefulness of antibiotics in active UC or CD and also in relapsing quiescent CD (Pineton de Chambrun *et al*., 2008). Antibiotics when used with 5-ASAs or corticosteroids or probiotics or immunosuppressive showed better effects than monotherapy. Metronidazole, ciprofloxacin, anti tuberculosis or the combinations of these antibiotics seem effective in CD. In UC, concurrent use of amoxicillin, tetracycline and metronidazole keeps patients in remission much better than monotherapy. New antibiotics such as anti-tuberculosis, macrolides clarithromycin, fluroquinolones, 5-nitroimidazoles, rifaximin, rifamycin derivatives (rifampin), aminoglycosides (tobramycin), rifabutin, clofazimine, tetracyclines (tetracycline and doxycycline) and vancomycin have shown some benefits in UC and CD. Up to now, most of supports go to use of ciprofloxacin and metronidazole. Rifaximin has also received good supports in management of CD. Regarding pharmacoeconomics essentials, low cost and toxicity antibiotics such as first to third generation of cephalosporin and gentamicin (effective against *E. coli*) or penicillin and clindamycin (effective against *C. difficile*) should be trailed in future trials. The final point is that the debate on the use of antibiotics in IBD still remains and need further well-designed studies to help identify which patients need antibiotic or antibiotic combination and if yes, what is the preferred compound with what dosage and duration of treatment.

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